REMARKS

The Applicants wish to thank the Examiner for his consideration of their previous remarks and for the removal of the rejections made in points # 9 and # 11 of the previous office action.

Claims 1-36 are pending. Claims 8 and 33 have been amended to add a period. Claim 35 has been amended to eliminate the term "in need thereof" as being unnecessary. Claims 1 and 34-35 have been amended to substitute the term "heterocyclic alkyl" for "alicyclic." This change does not narrow the scope of the claims, as it merely further clarifies the term "alicyclic" as used in these claims. Claims 1 and 34-35 were amended to eliminate the use of the term "prodrug." Claim 1 was amended to eliminate provisos 13) and 14); to carve out certain members from the L Markush group; and to eliminate provisos deemed unnecessary after carving out the L Markush group. Claims 9-12 and 29 were amended in order to align with amended claim 1. Claims 3-7 and 36 are cancelled in this Amendment. Claims 3-6 were cancelled due to the amendments to claim 1. Claims 37-70 are added in this Amendment.

Claims 37-68 carve out certain members from the J Markush group. Support for these claims can be found in original claims 1-33.

Support for new claims 69 and 70 can be found throughout the specification, *e.g.* at p. 24, lines 19-28 and in claim 1 of the 60/187,750 priority application.

Claims 1-6 and 8-36 stand rejected. Claim 7 was previously withdrawn from consideration as being drawn to a non-elected invention and is currently cancelled without prejudice.

None of the above changes raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

1. having been altered in any way for any reason related to patentability;
2. having been narrowed;

3. a concession that the invention as patented does not reach as far as the original, unamended claim;

4. a surrender of any subject matter as a condition of receiving a patent; and/or,

5. estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen.

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

I. EXAMINER'S GENERAL COMMENTS REGARDING THE DECLARATION OF DR. MARK ERION (POINT 4)

The Applicants had an interview with Examiner McKenzie and Supervisory Patent Examiner Shah on September 10, 2003 regarding application nos. 09/518,501 and 09/747,182. During the Interview on September 10, 2003, the Applicants discussed the rejections in the 09/518,501 case based on the term "prodrug." The Applicants explained that the term "prodrug" is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement.

The Examiner states that he finds the Declaration of Dr. Erion insufficient to overcome the rejections of claims 1-6 and 8-36 based on indefiniteness and lack of enablement because:

> the declaration contains no new data or references supporting Applicants assertions. The points in sections 4, 5, and 7-10 contain no data but rather only allegations of the Applicant. Mere allegations are not probative. (citations omitted)
>
> In point # 6, Dr. Erion offers an opinion based on the data published in Shaw (Pharm. Res.). Shaw (Pharm. Res.) describes experiments correlating results from *in vitro* assay using half-life determinations of eight compounds in dog intestinal homogenate and the pharmokinetics of the eight compounds after oral dosing in dogs. This is not persuasive for three reasons. Nowhere in the present specification is any *in vitro* assay in dog intestinal homgenate disclosed. Have any of Applicants' prodrugs of the compounds of formula (I) even been tested in this protocol? As discussed below in the enablement rejection, the two *in vivo* assays used by Applicants in support of prodrug enablement appear prophetic and have

> nothing to do with the experiments described in Shaw (Pharm. Res.). Secondly, it is unclear that compounds 2-9 of the reference are properly called prodrugs. The AUC is the total amount of drug effectively delivered to the serum of the dogs by an particular compound after oral dosing. The AUC of compounds 2-9 is only 16-31% of the amount delivered by the parent active ingredient compound 1, when compound 1 is administered alone. The peak concentrations of the active substance are only 3-17% of that achieved when compound 1 is administered alone. This would not appear to be a therapeutically effective amount. Thirdly, there is a ten-fold variation of the measured half-life of the eight compounds **2-9** *in vitro* in dog intestinal homogenate. Yet there is less than a two-fold variation in terminal half-life for the same compounds when tested *in vivo*. Compound **5** has one of the two shortest measured half-lives *in vitro*. Yet compound 5 has the fourth longest half-life measured *in vivo*. Correlation between *in vitro* and *in vivo* half-lives in this study would appear to be poor.
>
> In point #8 of the declaration, Dr. Erion points to pages 98-108, asserting that passage describes how to make the prodrugs of formula I. In fact, that passage appears to describe the synthesis of compounds of formula I, not prodrugs of the compounds of formula I. (Office Action pp. 3-4)

The Applicants wish to address some of the Examiner's assertions.

As to Dr. Erion's Declaration paragraph 6, it states:

> In some cases, the mechanism for activation of the prodrug is well understood making it even easier to test for conversion to the biologically active drug. For instance, an article in *Pharm. Res.* (Exhibit 1) reveals that concentrations of the prodrug bis(POM)-PMEA and its metabolites mono(POM)-PMEA and PMEA were determined using a reversed-phase HPLC method. The activation of the prodrug was confirmed by incubating the prodrug with carboxylesterase. [Erion Decl. ¶ 6]

The Applicants were not trying to imply that they did any testing in dogs. The Applicants were merely trying to show that a person of ordinary skill in the art can easily determine what is or what is not a prodrug. The Applicants note that the concentration values for the prodrugs are the plasma levels when administered orally. The plasma levels of the parent active ingredient, compound 1, were shown for when compound 1 was administered iv. Table 4 clearly indicates the 2 different routes of administration. Oral administration is usually the patient preferred means of drug intake (rather than iv administration). Any oral bioavailability over 10% is considered good. Additionally, the prodrugs also showed a longer half-life *in vivo* (except compounds 6 & 8) than the parent active ingredient compound.

Therefore, they would be effective longer in the plasma than the parent active ingredient. Indeed, with a longer half life, an effective dose orally would be lower than that administered iv.

Based on the September 10, 2003, interview, the Applicants believe that they overcame the same rejections based on the term "prodrug" in the 09/518,501 case and that likewise the same rejections should be overcome here. Therefore, the Applicants maintain that claims 1-6, 8-36 are definite, enabled, and satisfy the written description requirement. However, in order to advance the prosecution of this case, the Applicants have amended claims 1 and 34-35 to eliminate the term "prodrug."

II. THE RESTRICTION/ELECTION REQUIREMENT (POINTS 5 AND 6)

The Examiner states that claim 7 is drawn to a non-elected invention and must be cancelled and that the Applicants' last Response did not properly cancel claim 7.

The Applicants herewith cancel claim 7 without prejudice. Applicants reserve the right to pursue the subject matter of non-elected claims in this or any appropriate patent application.

The Examiner objects to claims 1-6, 8-29, and 31-36 as containing non-elected subject matter. The Examiner goes on to say:

> The claimed compounds, compositions, and methods that employ them present a variable core. Formula I(b) contains compounds drawn to the non-elected inventions with X other than carbon. Formula I(a) is drawn to non-elected inventions. (Office Action p. 5)

The Examiner indicates that the Applicants did not traverse this objection.

The Applicants noted that no claims have been allowed and will amend the claims as appropriate when they are allowed. The Applicants maintain that they will amend the claims as appropriate when they are allowed.

III. TITLE (POINT 7)

The Examiner makes objects to the title saying that after the election the title of the invention is not descriptive. The Examiner suggests replacing the phrase "Novel Aryl" with "Phenyl Phosphonate."

The Applicants respectfully disagree with the Examiner's objection, since the term aryl encompasses the term phenyl. MPEP § 606 merely requires that the title be technically accurate and descriptive. The Applicants believe that the current title meets those requirements, because the claimed compounds are aryl compounds.

IV. PRIORITY (POINT 8)

The Examiner acknowledges the Applicants' claim for priority under 35 U.S.C. 119(e). The Examiner then says that :

> However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1, 2, 4-6, 8-11, and 14-36 of this application. Applicants' present formula (I) is far broader than formula (I) of 60/187,750. For example, presently L can be a linking phenyl group. In the provisional application the cyclic linking group was limited to seven specific heteroaryl rings but not phenyl. Thus, the effective filing date of these claims is 3/7/01. (Office Action pp. 5-6)

The Applicants respectfully traverse. Since no claims have been allowed at this time, the Applicants can not determine which claims will have priority to the provisional application. In addition, newly added claims 69-70 clearly have the same scope as claim 1 of the 60/187,750 priority application.

V. THE 35 U.S.C. § 112, SECOND PARAGRAPH REJECTIONS

A. Claims 1-6, 8-17, 19, 26, 30, and 34-36 remain rejected as indefinite (Point 9)

The Applicants respectfully traverse this rejection.

The Examiner argues that the term "optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate" is indefinite. The Examiner says:

> Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine the claim term...the term "alicyclic" in claim 1 is used by the claim to mean "alicyclic, saturated heterocyclic, and aromatic", while the accepted meaning is "any aliphatic compound that contains a ring of carbon atoms", BioTech's Life Science Dictionary, copyright 1995-1998. The Condensed Chemical Dictionary defines the term as "..carbon atoms in closed ring structures". An alicyclic ring may contain multiple bonds but may not be aromatic and may not contain any heteroatoms." The term is indefinite because the specification does not clearly redefine the term. (Office Action pp. 6-7)

The Examiner goes on to say that the Applicants made four arguments.

> Firstly, they correctly assert that case law indicates that they may be their own lexicographers. Secondly, they point to lines 17-21, page 5 for the definition of "alicyclic". Thirdly, they quote further form the MPEP §2173.05(a). Fourthly, they point to a paper in a scientific journal JOC to

show that piperdine, piperazine, and morpholine are called, by the Spanish authors of the paper, "secondary alicyclic amines". (Office Action p. 7)

The Examiner says that he finds the argument unpersuasive, saying:

According to USPTO policy, the basis of this rejection has changed from whether the definition used by Applicants is repugnant to the skilled organic chemist, which was at issue in *In re Hill* (citation omitted), to the presently used analysis as to if the disputed term is clearly redefined. As discussed in the next point, "alicyclic" is not clearly redefined by Applicants. Secondly, lines 17-21, page 5 use open language "includes" and "but is not limited to". What other structures are included in their definition? Lines 17-21, page 5 fail to clearly redefine the term. Thirdly, Applicants' themselves fail to quote the most recent version of last paragraph MPEP §2173.05(a) in its' entirety,

"TERMS USED CONTRARY TO THEIR ORDINARY MEANING MUST BE CLEARLY REDEFINED IN THE WRITTEN DESCRIPTION Consistent with the well-established axiom in patent law that a patentee or applicant is free to be his or her own lexicographer, a patentee or applicant may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings if the written description clearly redefines the terms. See, e.g., *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) ("While we have held many times that a patentee can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning," in such a situation the written description must clearly redefine a claim term "so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term."); *Hormone Research Foundation Inc. v. Genentech Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990). Accordingly, when there is more than one definition for a term, it is incumbent upon applicant to make clear which definition is being relied upon to claim the invention. Until the meaning of a term or phrase used in a claim is clear, a rejection under 35 U.S.C. 112, second paragraph is appropriate. It is appropriate to compare the meaning of terms given in technical dictionaries in order to ascertain the accepted meaning of a term in the art. *In re Barr*, 444 F.2d 588, 170 USPQ 330 (CCPA 1971).

Applicants fail to make clear how they intend to redefine the standard chemical term "alicyclic". Fourthly, piperdine, which contains a single secondary amino nitrogen atom, is called by the Spanish authors of the JOC paper, a "secondary alicyclic amine". It is hard to see how such usage would indicate that "alicyclic" by itself, without the modifiers "secondary" and "amine" used in the JOC paper would be understood by the average chemist to include piperdine. The Examiner cited a dictionary in the previous office action is accordance with *In re Barr* (citation

> omitted). How does the isolated usage in a single paper by a non-native speaker of English indicate that this dictionary definition is incorrect? (Office Action pp. 8-9)

The Examiner admits that "Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine the claim term." (Office Acton p. 6) The Examiner says the term is not clearly redefined in the specification, but on the contrary, Applicants have clearly defined the meaning of the term "alicyclic" in the specification:

> The term "alicyclic" means compounds which combine the properties of aliphatic and cyclic compounds. Such cyclic compounds include but are not limited to, aromatic, cycloalkyl and bridged cycloalkyl compounds. The cyclic compound includes heterocycles. Cyclohexenylethyl and cyclohexylethyl are suitable alicyclic groups. Such groups may be optionally substituted. p. 5

A person of ordinary skill in the art reading the definition on p. 5 would clearly understand what compounds are meant by the term "alicyclic."

The use of open language within the definition of the term "alicyclic" does not mean that the Applicants have not clearly defined the term, since a person of ordinary skill in the art would understand what compounds are meant. In regards to the open language, the Examiner asks "What other structures are included in their definition?" (Office Action p. 7) The list of "aromatic, cycloalkyl and bridged cycloalkyl compounds" is meant to be exemplary. A person of ordinary skill in the art would understand what compounds are cyclic and what compounds are not cyclic.

The Examiner asks "How does the isolated usage in a single paper by a non-native speaker of English indicate that this dictionary definition is incorrect?" (Office Action p. 9) The Applicants are not saying that the dictionary definition is incorrect, but instead attempting to show that some persons of ordinary skill in the art may use the term to apply more broadly. The key is whether or not a person of ordinary skill in the art, upon reading the specification, would understand the scope of what is claimed. Here, a person of ordinary skill in the art would understand the term "alicyclic" and be able to determine the scope of what is claimed.

As the Examiner has acknowledged, numerous Federal Circuit decisions support the concept of the Applicants being their own lexicographers. *See e.g. Jack Guttman Inc. v. Kopykake Enter. Inc.*, 64 U.S.P.Q.2d 1302, 1307 (Fed. Cir. 2002)(saying where, as here, the patentee has clearly defined a claim

term, that definition "[u]sually is dispositive; it is the single best guide to the meaning of a disputed term."(quoting *Vitrionics Corp. v. Conceptronic, Inc.*, 39 U.S.P.Q.2d 1573,1577 (Fed. Cir. 1996)); *Trintec Indus. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597, 1599 (Fed. Cir. 2002)(citing *Markman* and saying the inventor may act as his own lexicographer and use the specification to supply implicitly or explicitly new meanings for terms); *CCS Fitness Inc. v. Brunswick Corp.*, 62 U.S.P.Q.2d 1658, 1662 (Fed. Cir. 2002)(stating that the claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term); *Rexnord Corp. v. Laitram Corp.*, 60 U.S.P.Q.2d 1851, 1854 (Fed. Cir. 2001)(stating that patent law permits the patentee to choose to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term that could differ in scope from that which would be afforded by its ordinary meaning); *Hockerson-Halberstadt Inc. v. Avia Group Int'l Inc.*, 55 U.S.P.Q.2d 1487, 1490 (Fed. Cir. 2000)(quoting "it *is always* necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning[because the specification] acts as a dictionary when it expressly defines terms" (*Southwall Techs., Inc. v. Cardinal IG Co.*, 34 U.S.P.Q.2d 1673, 1676 (Fed. Cir. 1995)); *Renishaw plc v. Marposs Societa' per Azioni*, 48 U.S.P.Q. 1117, 1121 (Fed. Cir. 1998)(stating that when an applicant elects to be his own lexicographer by providing an explicit definition, the definition selected by the patentee controls).

The Federal Circuit even reiterated this position in its seminal case on claim construction, *Markman v. Westview Instruments*. In that case, the Federal Circuit said: "As we have often stated, a patentee is free to be his own lexicographer. The caveat is that any special definition given to a word must be clearly defined in the specification." *Markman v. Westview Instruments*, 52 F.3d 967, 980; 34 U.S.P.Q.2d 1321, 1330 (Fed. Cir. 1995)(*en banc*)(internal citations omitted). The Applicants have clearly defined the term "alicyclic" in the specification. Since the Applicants have elected to be their own lexicographers, their definition controls.

As stated in MPEP § 2173, the primary purpose of the requirement for definiteness "is to ensure that the scope of the claims is clear so that the public is informed of the boundaries of what constitutes infringement of the patent." The Applicants have clearly informed the public of the boundaries of their claims by defining the term "alicyclic" in the specification.

The Examiner refuses to find the Applicants explicit definition meets the standards of 35 U.S.C. § 112, second paragraph in essence because it differs from the standard definition. Based on the Examiner's standard, one could never be their own lexicographer. The Examiner is simply ignoring the

well established axiom of patent law that Applicants can make their own definitions and satisfy the definiteness requirements.

However, in order to advance the prosecution of this case, the Applicants have amended claims 1 and 34-36 to substitute the term "optionally substituted heterocyclic alkyl where the cyclic moiety contains a carbonate or thiocarbonate" for the term "optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate." The Applicants believe that this term merely further clarifies the term "alicyclic" as used in these claims and does not add new matter. Nor does this amendment change the scope of the claims since the cyclic moiety must contain a carbonate or thiocarbonate, which necessarily limits the form of the cyclic groups.

The Applicants respectfully submit that Claims 1-6, 8-17, 19, 26, 30, and 34-36 are definite and request withdrawal of the rejection.

B. Claims 1-6 and 8-36 remain rejected as indefinite (Point 10)

The Applicants respectfully traverse this rejection.

The Examiner contends that the term "prodrug" is indefinite. The Examiner states that:

> Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. In the discussion of enablement of the prodrug, the Examiner cites references showing the lack of recognition in the art of medicinal chemistry of what structurally constitutes a prodrug.
>
> The Examiner suggest deleting the word prodrug. (Office Action p. 9)

The Examiner goes on to say that he believes the Applicants have made five arguments:

> Firstly, they assert that prodrug development is routine. Secondly that the open language used in the specification to describe the structures of their claimed prodrugs is permitted. Thirdly, the specification contains adequate definitions of "acyl" and "aryl", which in turn, were used in the definition of prodrug. Fourthly that the meaning of prodrug is both clear and art-recognized. Fifthly, that prodrug is a limitation used in a number of US Patents. Only the third point is persuasive. (Office Action p. 10)

The Examiner goes on to say why he finds the arguments unpersuasive:

> To the first point, assertion is not evidence and the question of the routine nature of prodrug discovery is an enablement issue, not an issue of the structures of Applicants' claimed compounds. The question is not whether such compounds may be found but rather if the average organic chemist can envision the structures of the claimed derivatives from the single word prodrug. While open language is routine in patent specifications, when it is used to change the meaning of a standard term, then a clear definition is required. To the fourth point, in the present case there is dispute as to the meaning of the concept of prodrug as well as to the structures implied by the term. The American Heritage® Dictionary of the English Language: Fourth Edition, 2000 defines a prodrug as "An inactive precursor of a drug, converted into its active form in the body by normal metabolic processes". This is a different meaning than used by Applicants. Applicants elsewhere argue that the metabolic process used to establish whether any compound is a prodrug can be done *in vitro* rather than "in the body". Do Applicants believe that a prodrug itself must be biologically inactive? However, even if the dispute as to the concept of prodrug is resolved, that will not resolve the question of the structures of the claimed prodrugs, which is the heart of the rejection.
>
> As to the fifth point, the indefiniteness remains despite what was allowed in another case. (citations omitted) (Office Action pp. 10-11)

The Applicants had an interview with Examiner McKenzie and Supervisory Patent Examiner Shah on September 10, 2003 regarding application nos. 09/518,501 and 09/747,182. During the Interview on September 10, 2003, the Applicants discussed the rejections in the 09/518,501 case based on the term "prodrug." The Applicants explained that the term "prodrug" is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement.

The Applicants believe that they overcame the same rejections based on the term "prodrug" in the 09/518,501 case and that likewise the same rejections should be overcome here. Therefore, the Applicants maintain that claims 1-6, 8-36 are definite. However, in order to advance the prosecution of this case, the Applicants have amended claims 1 and 34-35 to eliminate the term "prodrug."

In view of the above, the Applicants respectfully request withdrawal of this rejection.

VI. THE 35 U.S.C. § 112, FIRST PARAGRAPH REJECTIONS

A. Claims 1-6 and 8-36 remain rejected as not enabled (Point 11)

The Applicants respectfully traverse this rejection.

The Examiner says the claims "are not enabled for using prodrugs." (Office Action p. 12. The Examiner then cites the factors to be considered in making an enablement rejection and then goes on to say:

> a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, the second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting passes the threshold of undue experimentation.
>
> b) The direction concerning the prodrugs is found in The guidance concerning the prodrugs in the specification is found in formulas VI-VIII in pages 30-31, in the passage beginning at line 20, page 100, and more specifically in the passage spanning line 11, page 11 to line 26, page 15. The passage beginning at line 20, page 100 is labeled synthesis of prodrugs but in fact, outlines synthesis of formula (I) and does not provide any guidance to the structures of those out that scope. There are nine types of prodrugs disclosed in the passage spanning line 11, page 11 to line 26, page 15. Most are covered by formula (I) but Formula B, page 11, the right side of Formula E, page 13, Formulas E1,E-2. E3-. and F, page 14, the trichloroethyl ester in the last paragraph on page 15 are outside the scope of formula (I) and constitute the only guidance in the specification as to which compounds, not embraced by formula (I), are prodrugs of formula (I).
>
> c) Examples 17 and 18, page 130-131, lack any chemical data characterizing the products, and fail to specify the staring [sic] materials used, stating only an "aminoacid ester" is to be used. The two examples give no biological data and do not offer any evidence whether the products of these reactions are or are not prodrugs. Thus, these are prophetic, not working examples. In addition, as discussed above, these do not bear on the question of compounds lying outside the scope of formula (I). In Example I, spanning pages 138-139, Applicants describe a protocol for determining if a compound is a prodrug in rats. There are no results

reported and it is unclear if any of the compounds lying outside the scope of formula (I) have been tested in this protocol. In Example N, spanning pages 140-141, Applicants describe a second protocol for determining if a compound is a prodrug in rats. There are no results reported and it is unclear if any of the compounds lying outside the scope of formula (I) have been tested in this protocol. Thus, Applicants have provided no working examples of a prodrug.

d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body.

e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph.D. degree and several years of industrial experience.

g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*...Sanchez (J. Med. Chem.) in the four sentences spanning page 1766 implies that the prodrug nature of an alanate ester was only found empirically after the compound was made. Serafinowska (J. Med. Chem.) in the last complete paragraph on the left side of page 1375 describes the synthesis of thirty-eight potential prodrug phosphonate esters and two amides. Nineteen of these displayed measurable bioavailability. Of these, only seven had bioavailability greater than 10% required of a successful prodrug. It appears that only three of these substances were further evaluated as possible prodrugs. Thus, the skill in the art of synthesis of prodrugs would appear low and not predictable as of 1995.

Bundgaard (J. Med. Chem.) in the second sentence states that a major problem exists in prodrug design, namely designing the proper derivative. The second paragraph makes the point that some ethyl ester prodrugs are hydrolyzed *in vivo* and some are not. Thus, establishing the lack of predictability in the prodrug area as of 1987. Banker (Modern

Pharmaceutics) says on page 451, first paragraph that "preparation of prodrugs is becoming a common practice", implying that is not routine as of 1996. Banker (Modern Pharmaceutics) says on page 596, third paragraph that "extensive development must be undertaken to find the correct chemical modification". Clearly an invitation to open-ended and potentially inconclusive research.

Wolff (Medicinal Chemistry) ins second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success of preparing prodrugs. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard protocol discussed in the last sentence of this paragraph is particularly relevant. Finally, concerning the amine containing drugs, Shan (J. Pharmaceutical Sci.) indicates in the first paragraph, page 765 that "[a]pplying similar strategies to the preparation of prodrugs of amine-containing drugs is somewhat more problematic...because of the stability of the amide bond". Thus indicating that the research program outlined above may be inconclusive when applied to drugs that are amines.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1.

Thus, undue experimentation will be required to determine if any particular derivative of formula I is, in fact, a prodrug. (Office Action pp. 12-17)

The Examiner then continues:

Applicants argue that working examples are not required for enablement, Applicants assert that the experimentation to develop a prodrug is routine, and thirdly, point to the advanced age of the references used by the Examiner is his analysis of the state of the art. Firstly, as discussed above lack of working examples, which Applicants admit to be the case in the present application, is one of the eight factors to be used in reaching a conclusion concerning enablement and any conclusion as to whether the experimentation required is undue. Secondly, whether undue experimentation is required is a conclusion to be reached after an analysis of the facts. It itself, is not a fact to be disputed or simply asserted. Applicants themselves address only two of the eight factors used to reach such a conclusion. Thirdly, three of the references used by the Examiner were kindly supplied by the Applicants to bolster their argument for enablement. These three are Sanchez (J. Med. Chem.), Serafinowska (J. Med. Chem., Ref. CJ), and Bundgaard (J. Med. Chem.). Presumably Applicants thought they did accurately describe the state of the art when they supplied them to the Examiner. If Applicants have more up to date references concerning the state of the art of prodrug discovery, then such

> references would be a welcome addition to the facts used as one of the eight factors required by (citations omitted). In the absence of such up to date material, the age of the Examiners references does not invalidate them. (Office Action pp. 17-18)

The Applicants had an interview with Examiner McKenzie and Supervisory Patent Examiner Shah on September 10, 2003 regarding application nos. 09/518,501 and 09/747,182. During the Interview on September 10, 2003, the Applicants discussed the rejections in the 09/518,501 case based on the term "prodrug." The Applicants explained that the term "prodrug" is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement.

The Applicants believe that they overcame the same rejections based on the term "prodrug" in the 09/518,501 case and that likewise the same rejections should be overcome here. Therefore, the Applicants maintain that claims 1-6, 8-36 are enabled. However, in order to advance the prosecution of this case, the Applicants have amended claims 1 and 34-35 to eliminate the term "prodrug."

In view of the above, the Applicants respectfully request withdrawal of this rejection.

B. Claims 1-6 and 8-36 are newly rejected as not enabled (Point 12)

The Applicants respectfully traverse this rejection.

The Examiner appears to be making the same rejection as in VII.A. above, *i.e.* claims 1-6 and 8-36 are not enabled for use of the term "prodrug." The Examiner says:

> Applicants are not enabled for making prodrugs of the compounds of formula (I). Nowhere in the specification are directions given for preparing "prodrugs" of the claimed compounds. Since structures of these "prodrugs" are uncertain, direction for their preparation must be even more unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitutes instructions to the BS process chemist of how make a compound. (Office Action p. 18-19)

The Applicants had an interview with Examiner McKenzie and Supervisory Patent Examiner Shah on September 10, 2003 regarding application nos. 09/518,501 and 09/747,182. During the Interview on September 10, 2003, the Applicants discussed the rejections in the 09/518,501 case based on the term "prodrug." The Applicants explained that the term "prodrug" is well-understood and

enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement.

The Applicants believe that they overcame the same rejections based on the term "prodrug" in the 09/518,501 case and that likewise the same rejections should be overcome here. Therefore, the Applicants maintain that claims 1-6, 8-36 are enabled. However, in order to advance the prosecution of this case, the Applicants have amended claims 1 and 34-35 to eliminate the term "prodrug."

In view of the above, the Applicants respectfully request withdrawal of this rejection.

C. Claim 36 remains rejected as not enabled (Point 14)

The Examiner contends that while the specification is enabling for treatment of diabetes, it is not enabling for treatment of "glycogen storage diseases" generally. The Examiner states:

> Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assay, whose results are described in Table 3, page 133, and clinical efficacy against any specific disease. Case law is clear on this point. In an unpredictable art, such as diabeteis [sic] pharmacology, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy. (Office Action p. 21).

The Examiner goes on to say:

> Applicants have clarified that these diseases are the enzyme deficiency disorders of seven specific types of glycogenosis as (Cori classification) and as further described in Chen (Principles of Internal Medicine). The Table 347-1 on page 2178 of Chen (Principles of Internal Medicine) teaches that none of these diseases involves fructose-1,6-bisphosphaaste [sic]. The only glycogen storage disease involving fructose is type VII, Tarui disease. This disease is caused by a deficiency of the phosphofructokinase enzyme. The Figure 347-1 on page 2177 makes clear that this is a different enzyme than fructose-1,6-bisphosphaaste [sic]. Why do Applicants believe that their fructose-1,6- bisphosphaaste [sic] will be benefication for any of these enzyme disorders? (Office Action pp. 21-22)

The Examiner then says:

> Applicants argue that any compound which inhibits glycogen accumulation in the body would necessarily be effective in the treatment of "glycogen storage diseases". This is neither true nor on point.

> Applicants do not address the issues discussed in the preceding paragraph. Unless the mechanism of action of Applicants' compounds has some strong bearing upon the disease process, even if it inhibits glycogen storage by another mechanism, then it cannot affect the disease process. Six of the seven specific types of glycogenosis (Cori classification) have nothing to due [sic] with Applicants mechanism of action. The seventh type would be exacerbated, not improved by a compound acting by Applicants' mechanism. In any case, the standard is the correlation of the assays used to claimed disease. The standard is not whether Applicants compounds could hypothetically have such an action. (Office Action pp. 22-23)

The Applicants have cancelled claim 36 without prejudice. Therefore Applicants believe that is rejection is now moot.

D. Claims 1-6 and 8-36 are newly rejected as lacking written description (Point 13)

The Applicants respectfully traverse this rejection.

The Examiner finds that the term "pharmaceutically acceptable prodrugs and salts thereof" does not meet the written description requirement. The Examiner says:

> The phrase "pharmaceutically acceptable prodrugs...thereof" describes the function of the claimed derivatives but provides no structural guidance to the average medicinal chemist indicating that the average medicinal chemist would recognize the applicant had possession of the claimed invention. (Office Action p. 19)

The Examiner then quotes from MPEP § 2163 I and then says "What are the chemical formulas of the claimed prodrugs?" (Office Action p. 20) The Examiner recites further quotations from MPEP § 2163 I and then says:

> In the present case, Applicants have even failed to provide us with a method of preparing the claimed prodrugs, merely with a description of what they are supposed to do. Where is the evidence of the correlation between the function "prodrug" and the structure of the derivatives that provide that function? (Office Action p. 21)

The Applicants had an interview with Examiner McKenzie and Supervisory Patent Examiner Shah on September 10, 2003 regarding application nos. 09/518,501 and 09/747,182. During the Interview on September 10, 2003, the Applicants discussed the rejections in the 09/518,501 case based on the term "prodrug." The Applicants explained that the term "prodrug" is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah

indicated that this language does meet the requirements for definiteness, written description, and enablement.

The Applicants believe that they overcame the same rejections based on the term "prodrug" in the 09/518,501 case and that likewise the same rejections should be overcome here. Therefore, the Applicants maintain that claims 1-6, 8-36 satisfy the written description requirement. However, in order to advance the prosecution of this case, the Applicants have amended claims 1 and 34-35 to eliminate the term "prodrug."

In view of the above, the Applicants respectfully request withdrawal of this rejection.

E. Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 remain rejected as lacking written description (Point 15)

The Applicants respectfully traverse this rejection.

The Examiner says:

> The two provisos in the next to last three lines of claim 1 lack written description. Nowhere in the specification is such a relationship linking the description among radical R^5 and radicals J^2-J^6 described. Such a negative limitation requires description. In *Ex parte Grasselli*, et al. 231 USPQ393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts." (Office Action p. 23)

The Examiner goes on to characterize the Applicants' arguments as follows:

> Applicants argue that removal of elements from a Markush list of claim limitations is a permitted practice. Secondly, they attempt top [sic] factually distinguish their proviso from *Ex parte Grasselli, et al.* 231 USPQ 393, stating that no Markush list was present in *Ex parte Grasselli, et al.* 231 USPQ 393. This is not persuasive. (Office Action p. 24)

The Examiner then explains why he did not find the Applicants' argument persuasive:

> Applicants did not remove any elements from the Markush lists describing radical R^5 and radicals J^2-J^6. What they did was exclude two specific species by creating a new relationship among these radicals. Until the

> Examiner made the anticipation rejection, the Applicant had no reason to single out the species embraced by the proviso. When filed, the application did not recognize that species as special, nor is the Applicant now claiming that he recognized it as so. Applicants are invited to remove items from the lists describing radical R^5 and radicals J^2-J^6.
>
> Since Applicants did not, in fact, remove items from a Markush list, the issue of whether *Ex parte Grasselli, et al.* 231 USPQ 393 removed such items need not be considered. (Office Action p. 24)

As stated in the MPEP § 2163, in order to "satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." In *In re Wertheim*, the Court said "[i]t is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosures that appellants invented processes for including those limitations." *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)(internal citations omitted). In *Wertheim*, the disputed term was the limitation "between 35% and 60%." *Id.* at 98. The specification recited a broader range of 25-60%. The Court found that the narrower limitation had adequate written description saying "we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of the appellants' invention." *Id.* The Court went on to say "[i]f lack of literal support alone were enough to support a rejection under § 112, then the statement of *In re Lukach*, that 'the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of § 112,' is empty verbiage." *Id.* (internal citations omitted).

In the previous response, the Applicants cited a more analogous case, where the applicants faced a 102 rejection unless they could claim the benefit of an earlier filed application. *In re Driscoll*, 195 U.S.P.Q. 434, 436 (C.C.P.A. 1977). The priority application had a Markush group wherein R was selected from the group consisting of 14 groups. *Id.* at 436. The claim in the application at issue allowed R to be only one of those 14 groups. *Id.* at 435. The Examiner and Board found that the applicants were not entitled to the earlier filing date, since they believed that the earlier application lacked an adequate written description for the new claim. *Id.* at 436.

The Court disagreed saying:

> We thus agree with appellant that a skilled artisan would recognize from the disclosure of S.N.782,756 fourteen distinct classes of compounds, each class having a single member of the R group at the 5-position of the

> thiadiazole moiety and variable substituent groups on the urea moiety. This being the case, it follows that S.N.782,756 describes the subject matter of claim 13 inasmuch as one of the fourteen classes of compounds is the 5-alkylsulfonyl-1,3,4-thiadiazole ureas defined therein. *Id.* at 437-38.

The Court went on to criticize the decision by the Examiner and the Board as "a hypercritical application" of the written description requirement. *Id.* at 438. The Court felt that upholding the Board's decision would create a predicament for future applicants where:

> If, when [applicants] yield any part of what they originally believed to be their due, they substitute a new "invention," only two courses will be open to them: they must at the outset either prophetically divine what the art contains, or they must lay down a barrage of claims, starting with the widest and proceeding by the successive incorporation of more and more detail, until all combinations have been exhausted which can by any possibility succeed. The first is an impossible task; the second is a custom already more honored in the breach than in the observance, and its extension would only increase that surfeit of verbiage which has for long been the curse of patent practice, and has done much to discredit it. It is impossible to imagine any public purpose which it could serve. *Id.* (internal citation omitted)

Such is the case here, adding a proviso that yields part of what was the originally claimed invention should not constitute new matter.

The Applicants have also distinguished the *Ex Parte Grasselli* case cited in that it appears that the specification in that case did not disclose a Markush group of possible catalysts and then only claim some of the catalysts in the later application. *Ex Pare Grasselli*, 231 U.S.P.Q. 393, 394 (Bd. Pat. App. & Int. 1983). Based on the facts of the case, it appears that the applicants added provisos eliminating certain catalysts found in the prior art, when they had not named possible catalysts before. *Id.* This Application is distinguishable in that the specification and claim 1 have disclosed Markush groups for R^5 and L. The proviso merely yields part of what was originally claimed. The proviso has not added new matter.

A person of skill in the art would understand that the Applicants had possession of the invention claimed in claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29. The provisos do not constitute new matter and do satisfy the written description requirement. However, in order to advance the prosecution of this Application, the Applicants have amended claim 1 to eliminate the provisos in question and cut out individual members of the Markush group for L. Claims 2-33 were amended to align with new claim 1.

The Applicants have also added new claims 37-68 that cut out individual members of the Markush groups for J, without narrowing the Markush group for L.

Therefore, Applicants respectfully request the removal of this rejection.

VII. THE 35 U.S.C. § 102 REJECTIONS

A. Claims 1-2, 8-9, 11-12, 14-15, 17, 20, and 29 are rejected under 35 U.S.C. § 102(b) as being anticipated by Biller ('153) (Point 16)

The Applicants respectfully traverse this rejection.

The Examiner says:

> There is one compound taught in this reference that fit formula (I) with one $R^1Y = {}^iPrO$, R^1 = isopropyl, the R^1Y = HO, R^1 = hydrogen, L = alkyleneoxyalkylene group $-CH_2-O-CH_2-$, R^5 = disubstituted phenyl, J^2 = methyl, and J^4 = 2,6-dimethyl-1,5-heptadienyl...The compound is found in lines 46-61, column 34. Applicants proviso 10) on page 5 of the recent set of pending claims excludes compounds with R^1 = alkyl when the other is hydrogen. However, the compound shown below may well be a prodrug of the compound with both R^1 = hydrogen. That compound is not excluded by the proviso. The compound with R^1 = hydrogen is the basis of the rejection. (Office Action p. 25)

The Examiner is correct in that R^1 can be selected from the lower alkyl only when the other YR^1 is $-NR^6-C(R^{12}R^{13})_n-C(O)-R^{14}$. The Applicants believe that the proviso excludes compounds of structure disclosed by Biller. It is irrelevant whether or not the structure is a prodrug of the compound where both R^1 = hydrogen, as these compounds have already been excluded by the proviso. The use of the term "prodrug" cannot add back in what has already been excluded. In any event, the Applicants have amended claim 1 to eliminate the use of the term "prodrug" from the phrase "and pharmaceutically acceptable prodrugs and salts thereof."

Because the structures were excluded by provisos, claims 1-2, 8-9, 11-12, 14-15, 17, 20, and 29 are not anticipated. Applicants respectfully request removal of this rejection.

B. Claims 1-3, 8-9, 11, 14-17 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Krecmerova (Point 17)

The Applicants respectfully traverse this rejection.

The Examiner states that:

> There is one compound taught in this reference that fit formula (I) with both R^1Y = HO, R^1 = hydrogen, L = alkyleneoxyalkylene group $-CH_2-O-CH_2-CH_2-$, R^5 = disubstituted phenyl, $J^3 = J^5$ = amino...The formula is

> found on page 662 and is structure **XVIII**. Synthesis is taught in the paragraph spanning pages 667-668. (Office Action p. 26)

The Applicants believe that the amended and new claims exclude this compound. In claim 1 and its dependent claims, L cannot be –alkeneoxyalklene-. In claim 37 and its dependent claims, J cannot be amino. Therefore, claims 1-3, 8-9, 11, 14-17 and 20 are not anticipated. Applicants respectfully request removal of this rejection.

C. Claims 1-2, 8, 14-17 and 19-20 are rejected under 35 U.S.C. § 102(b) as being anticipated by or in the alternative under 35 U.S.C. § 103(a) as obvious over Buss ('557) (Point 18)

The Applicants respectfully traverse this rejection.

The Examiner says:

> There is one compound taught in this reference that fit formula (I) with R^1Y = $MeNR^6$, R^1 = R^6 = methyl, R^1 = R^6 = hydrogen, L = -1,4-imidazoyl-, R^5 = trisubstituted phenyl, J^2 = J^3 = J^4 = chlorine. The compound is found in the Table in column 9, as entry 39. Applicants' proviso 6) and proviso 10) on page 5 of the recent set of pending claims excludes compounds with R1 = alkyl when the other is hydrogen. However, the compound shown below may well be a prodrug of the compound with both R^1Y = HO. That compound is not excluded by the proviso. The compound shown below may well be a prodrug of the compound with one R^1Y = HO and the other R^1Y = NH_2. That compound is also not excluded by the proviso. When Applicant claims a compound in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/102 rejection. *In re Best*, 195 USPQ 430. (Office Action pp. 26-27)

The Examiner is correct in that the Buss compound is eliminated by provisos 6) and 10). It is irrelevant whether or not the structure is a prodrug of the compound where R^1Y = HO and the other R^1Y = NH_2, as these compounds have already been excluded by the proviso. The use of the term "prodrug" cannot add back in what has already been excluded. In any event, the Applicants have amended claim 1 to eliminate the use of the term "prodrug" from the phrase "and pharmaceutically acceptable prodrugs and salts thereof."

Because the structures were excluded by provisos, claims 1-2, 8, 14-17 and 19-20 are not anticipated or obvious. Applicants respectfully request removal of this rejection.

D. Claims 1-2, 8, 14-17 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by or in the alternative under 35 U.S.C. § 103(a) as obvious over Huang (Point 19)

The Applicants respectfully traverse this rejection.

The Examiner says:

> There is one compound taught in this reference that fit formula (I) with both R^1Y = EtO, R^1 = ethyl, L = -1,4-imidazoyl-, R^5 = disubstituted phenyl, $J^3 = J^4$ = methyl. The compound is found in the Table in page 511, as entry **2e**. Applicants' proviso 10) on page 5 of the recent set of pending claims excludes compounds with both R^1 = alkyl. However, the compound described may well be a prodrug of the compound with both R^1Y = HO. That compound is not excluded by the proviso. When Applicant claims a compound in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/102 rejection. *In re Best*, 195 USPQ 430. (Office Action pp. 27-28)

The Examiner is correct in that the Huang compound is excluded by proviso 10). It is irrelevant whether or not the structure is a prodrug of the compound where both R^1Y = HO, as these compounds have already been excluded by the proviso. The use of the term "prodrug" cannot add back in what has already been excluded. In any event, the Applicants have amended claim 1 to eliminate the use of the term "prodrug" from the phrase "and pharmaceutically acceptable prodrugs and salts thereof."

Because the structures were excluded by provisos, claims 1-2, 8, 14-17 and 20 are not anticipated or obvious. Applicants respectfully request removal of this rejection.

E. Claims 1-2, 8-11, 14-15, 17, 20 and 29 are rejected under 35 U.S.C. § 102(e) as being anticipated by Duffy (WO 20011089457) (Point 20)

The Applicants respectfully traverse this rejection.

The Examiner says:

> There are four compounds taught in this reference that fit formula (I). The one shown below has both R^1Y = HO, R^1 = hydrogen, L = -1,3-phenyl-, R^5 = disubstituted phenyl, J^2 = methoxyl, R^{11} = methyl, and J^5 = chlorine. It has Registry Number 118847-92-0 and is found in the reference in line 19, page 26. The other compounds are in line 5, page 25, line 24, page 25, and line 5, page 26. (Office Action p. 28)

The Applicants believe that the amended and new claims exclude these compounds. In claim 1 and its dependent claims, L cannot be -phenyl-. In claim 37 and its dependent claims, J cannot be halo,

$-NH_2$, or $-NO_2$. Therefore, claims 1-2, 8-11, 14-15, 17, 20 and 29 are not anticipated. Applicants respectfully request removal of this rejection.

VIII. THE EXAMINER'S NEW MATTER REJECTION OF CLAIMS 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, AND 29 (POINT 21)

The Applicants respectfully traverse this rejection.

The Examiner acknowledges that claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 are novel over U.S. Patent No. 4,640,701 ("the '701 patent"). The Examiner then states that the provisos are new matter.

As explained above in VI.E, the provisos do not constitute new matter and do satisfy the written description requirement. However, in order to advance the prosecution of this Application, the Applicants have amended the claims to eliminate the provisos in question as explained in VI.E above. In addition, the new claims only contain provisos that were present in the original claims.

Therefore, Applicants respectfully request the removal of this rejection.

CONCLUSION

In view of the above remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

Respectfully Submitted,

Date: 3/8/04

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